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Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/943,048
Filing Date: August 30, 2001
Appellant(s): EL-NAGGAR et al.

EL-NAGGAR et al.
For Appellant

EXAMINER'S ANSWER

This is in response to the Appellant's Appeal Brief filed August 29, 2006 appealing from the Office action mailed March 01, 2006, in consideration of the Notice of Non-Compliant Appeal Brief mailed August 15, 2006 and the Advisory Action mailed May 26, 2006.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief contains a statement concerning related appeals or interferences.

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct

Claims 10-13, 15 and 18-24 are rejected. Claims 1-9, 14 and 16-17 are cancelled. This appeal involves claims 10-13, 15 and 18-24.

(4) Status of Amendments

The statement of the status of claims contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to Be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows: The rejection of claims 23-24 under 35 U.S.C. 112, first paragraph, and the rejection of claim 15 under 35 U.S.C. 112, second paragraph, are not presented for review on appeal because they have been withdrawn by the examiner (see infra 'Response to Argument' and line 5 of Advisory Action mailed on May 26, 2006).

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

WO 01/14705 A1 HEDDEN et al. 06-2001

DE 19855426 A1 LANGHOFF et al. 06-2000

US Patent No. 6,541,613 HENDLER et al. 04-2003

US Patent No. 6,444,221 SHAPIRO 09-2002

DRUG FACTS AND COMPARISON, 1995 EDITION, pp. 1248

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 10-13, 18-21 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hedden et al. (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6444221). This rejection is set forth in prior Office Action, mailed March 01, 2006.

Claims 15 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hedden et al. (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6444221), and further in view of Burch et al. (US 6552031) and Drug Facts and Comparison (1995 Edition, pp. 1248) and Hendeler (US 6541613B2). This rejection is set forth in prior Office Action, mailed March 01, 2006.

The claims 10-15 and 24 read on a method for treating inflammatory disorders in a mammal comprising administering concurrently a composition comprising (i) a standard therapeutic dose of a COX2 inhibitor selected from the group consisting of celecoxib and

rofecoxib, (ii) low dose aspirin in an amount of 70-85 mg and (iii) an antioxidant selected from the group consisting of a flavanoid, a flavonoid, and isoflavone, and combination thereof. The claims 18-22 read on a composition comprising (i) a standard therapeutic dose of a COX2 inhibitor selected from the group consisting of celecoxib and rofecoxib, (ii) low dose aspirin in an amount of 70-85 mg and (iii) an antioxidant selected from the group consisting of a flavanoid, a flavonoid, and isoflavone, and combination thereof. Further limitations include " flavanoid" (claims 11 and 19); "flavonoid" (claims 12 and 20); "isoflavone" (claims 13 and 21); "enteric coated" (claims 15 and 22).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-13, 18-21 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hedden et al. (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6444221).

Hedden teaches the use of COX-2 inhibitor such as celecoxib and rofecoxib for the treatment of inflammatory disorders including arthritis (page 2, line 16; page 3, line 6; page 19, lines 10-12).

Langhoff teaches the use of low dose aspirin (in dosage range of 30mg-75mg) for the treatment of anti-inflammatory disorder including rheumatism and arthritis (claims 18-19).

Shapiro (US 6444221) teaches the use of flavonoids, flavanoids and isoflavones (i.e., daidzin, genistein, quercetin, silymarin, etc...) as antioxidants having functional equivalent property for the treatment of inflammatory disease conditions including arthritis or rhuematoidal arthritis (column 9, line 52 thru column 10, line 32; column 20, line 47 thru column 21, line 8).

The teaching of Hedden differs from the claimed invention in combination use of said COX-2 inhibitor, low dose aspirin and flavanoids or isoflavones. To incorporate such teaching into the teaching of Hedden, would have been obvious in view of Langhoff who teaches the use of the low dose aspirin for the treatment of arthritis and Shaprio who teaches the use of flavonoids or flavones for inflammatory condition including arthritis.

Above references in combination make clear that COX-2 inhibitor such as rofecoxib and celecoxib, low-dose aspirin and antioxidants (i.e., flavanoid, flavonoid and isoflavone) have been individually used for the treatment of arthritis. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*

With respect to the claimed concurrent administration, those of ordinary skill in the art would have been readily optimized concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate administration regimen for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, in absence evidence to the contrary.

Claims 15 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hedden et al. (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6444221), and further in view of Burch et al. (US 6552031) and Drug Facts and Comparison (1995 Edition, pp. 1248) and Hendeler (US 6541613B2).

The modified teaching of Hedden includes all that is recited in claims 15 and 22 except the preparation of said combination in an enteric-coated formulation.

Burch and Drug Facts and Comparison being supplied as a reference to demonstrate the art recognized skill in preparing rofecoxib, low dose aspirin or antioxidants (i.e., isoflavones) in

enteric coating formulation (see column 18, line 31 thru column 23, line 3 of Burch; commercially available Bayer Low Adult Strength 81mg in Facts and Comparison; abstract and column 8, lines 38-49 of Hendler).

As discussed above, the modified teaching of Hedden differs from the claimed invention in the preparation of said composition in enteric coated formulation. However, it would have been obvious to one of ordinary skill in the art to arrive at the instantly claimed enteric coated formulation for the purpose of the regulation of release or for the protection of the formulation since the preparation of rofecoxib, aspirin or said antioxidant in enteric coatings is old and well known in the art. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

(10) Response to Argument

With respect to the rejection of claims 23-24 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement,

Appellant in his argument takes the position that the limitations in claims 23-24 of "wherein the low dose aspirin is not covalently attached to the COX2 inhibitor" inherently disclosed in the Appellant's specification, even if not explicitly disclosed, is not new matter (page 4, last paragraph to bridging paragraph in page 5 of Appellant's Brief on Appeal). In appellants' Response filed August 29, 2006, appellant stated:

Covalent attachment is a form of chemical binding. Therefore, in order for the low dose aspirin to be covalently attached to the COX2 inhibitor, the low dose aspirin must necessarily be chemically attached to the COX2 inhibitor by the covalent attachment. However, Par. [0024] of Appellants' specification recites: "The combined compounds of this invention may be formulated such that, although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized." Appellants assert that it is impossible for the low dose aspirin to both be chemically attached to the COX2 inhibitor and also have minimal physical contact with the COX2 inhibitor. Therefore, the preceding citation in Par. [0024] of Appellants' specification inherently discloses the low dose aspirin to not be chemically attached to the COX2 inhibitor and thus not be covalently attached to the COX2 inhibitor.

Par. [0024] of Appellants' specification further recites: "Still another approach would involve the formulation of combined compounds in which the one compound is coated with a sustained and/or enteric release polymer, and the other compound is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose or other appropriate materials as known in the art, in order to further separate the active components. **The polymer coating serves to form an additional barrier to interaction with the other component.**" (emphasis added). In the preceding embodiment of the present invention described in Par. [0024], the active ingredients are physically isolated from each other and prevented from interacting with each other, by the polymer coating, so that the active ingredients are not in covalent contact with each other. Therefore, the preceding citation in Par. [0024] of Appellants' specification inherently discloses the low dose aspirin to not be covalently attached to the COX2 inhibitor.

Appellant's argument is found persuasive. Accordingly, the rejection of claims 23-24 under 35 U.S.C. 112, first paragraph, has been withdrawn.

With respect to the rejection of claim 15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, the examiner determines that appellant's argument is found persuasive. Accordingly, the examiner's rejection of claim 15 under 35 USC 112, second paragraph, has been withdrawn (see also line 5 of Advisory Action mailed on May 26, 2006).

With respect to the rejection of claims 10-13, 18-21 and 23-24 under 35 U.S.C. 103(a) as being unpatentable over Hedden et al. (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6444221),

Appellant's argument takes the position that the low dose aspirin in the amount of 70-85mg is not taught or suggested in the examiner's cited references, particularly Langhoff (page 9, para. 3 of Appellant's Brief on Appeal). In appellants' Response filed August 29, 2006, appellant stated:

> However, none of the citations to Langhoff in Tables 1 and 2 teach or suggest that aspirin (i.e.,acetylsalicylic acid) having a dosage not exceeding 75 mg contributes to the treatment of rheumatic-arthritic diseases outside of Langhoff's disclosed composition.
>
> In addition, none of the citations to Langhoff in Tables 1 and 2 teach or suggest that aspirin having a dosage not exceeding 75 mg contributes, by itself, to the treatment of rheumatic-arthritic diseases.

Appellant's argument is not found persuasive because the Langhoff's disclosed dosage range (30-75mg) of acetylsalicylic acid (aspirin) "metes and bounds" the instantly claimed "70-85mg". Reading the entire specification of Langhoff, one having ordinary skill in the art would

have understood that the administration of between 30 and 75 mg per day of acetylsalicylic acid to the body would provide an anti-inflammatory effect, in particularly its effect in the treatment of rheumatic and arthritic disorders without concern for potential adverse effects (see page 2, lines 20-26, page 3, lines 25-28 and claim 18-19 of the translated DE 198 55 426 A1). Thus, the cited references in combination (Hedden in view of Langhoff and Shapiro) make obvious the instant invention of the claims 10-13, 18-21 and 23-24.

In response to the Appellant's argument that aspirin having a dosage not exceeding 80 mg does not contribute to the treatment of rheumatic-arthritic disease, particularly to the Appellant's contention that "Langhoff's Example does not support the use of aspirin in a dosage range of 30-75mg to treat inflammatory disorders in a mammal" (page 12, lines 12-14 and page 14, lines 11-13 of Appellant's Brief on Appeal), the examiner recognizes that the suggested or disclosed dosage range of the acetylsalicylic acid in Langhoff is lower than 75mg, not over 80mg. Langhoff discloses that acetylsalicylic acid in a concentration of lower than 75 mg would lead to the anti-inflammatory effect without known adverse effects of acetylsalicylic acid, such as gastric hemorrhages or pseudoallergic reactions.

As discussed in preceding comments, Langhoff teaches the anti-inflammatory enhancing effect of the lower dosage of acetylsalicylic acid (page 8, lines 1-12). For instance, composition of D (50% of A and 50% of B, which contains 40 mg of acetylsalicylic acid) shows a superior anti-inflammatory effect when compared to B composition (80 mg of acetylsalicylic acid in the form of separate component or A composition (10 g of cold liver oil, 1000 mg of vitamin E, 1000 mg of vitamin C in the forma of separate component). Thus, the skilled artisan, reading the

entire specification, would understood that the low dose of aspirin in dosage range of 30-75mg leas to an effect that enhances the anti-inflammatory action without known adverse effects of acetylsalicylic acid.

Appellant's argument in the response takes the position that it is known in the art that low dose aspirin in doses of 30-75 mg is not effective in the treatment of inflammatory disorder, as evidenced by numerous published papers (refers to Calin A. "Pain and Inflammation, Am J Med. 1984 Sep 10;77(3A):9-16; Gomes I, "Aspirin: a neuroprotective agent at high doses?", Natl Med J India. 1998, Jan-Feb; 11(1):14-7; Applerouth et al. "Comparison of the safety and efficacy of nabumetone and aspirin in the treatment of osteoarthritis in adults", Am J Med. 1987 Oct 30; 83(4B):78-81; Fries et al. "A reevaluation of aspirin therapy in rheumatoid arthritis", Arch Intern Med. 1993 Nov 8; 153(21):2465-2471; Edwards, W. "Etodolac, aspirin and placebo in patients with rheumatoid arthritis: a 12-week study", Clin Ther. 1983; 5(5):495-503; Kolarz, G. "Double-blind, cross-over, international multicentre investigation of two doses of indoprofen compared with ASA and placebo in rheumatoid arthritis", Eur J Rhuematol Inflamm., 1981; 4(1):53-59). The Appellant asserts that much higher doses of aspirin that 30-75 mg are required for therapeutically effective treatment of inflammatory disorder.

This argument is not found persuasive. As discussed above, the result of using low dose of aspirin (35-75mg) for the treatment of inflammatory disorder such as rheumatism and arthritis as taught in Langhoff is unexpected result distinguished from the prior art. The dosage range of acetylsalicylic acid (aspirin) that are generally disclosed or tested in the Appellant's supplied references is much higher than "30-75mg". There is no evidence in the supplied references that

30-75mg of acetylsalicylic acid is not going to be effective as anti-inflammatory agent. Contrary to the Appellant's argument, Langhoff clearly teaches (by Example) the anti-inflammatory enhancing effect of the lower dosage (30-75mg) of acetylsalicylic acid.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the examiner's cited references (Hedden, Langhoff and Shapiro) in combination make clear that the COX-2 inhibitor such as rofecoxib and celecoxib, the low-dose aspirin and antioxidants (i.e., flavanoid, flavonoid and isoflavone) have been individually used for the treatment of inflammatory diseases such as arthritis. Thus, the examiner maintains that it is obvious to combine compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. See *In re Kerkhoven, 205 USPQ 1069 (CCPA 1980). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (*Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.*); and Ex parte Quadranti,*

25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious).

In response to Appellant's argument in the response that the appealed claims 15 and 22 respectively depend from claims 10 and 18, which Appellants have argued supra, are not obvious over Hedden in view of Langhoff and Shapiro, and further in view of Burch, Drug Facts and Comparison and Hendler, the examiner recognizes that the argument in the brief is basically the same as discussed above, so the response discussed above applies here as well and is unpersuasive for reason just discussed.

(11) Related Proceedings Appendix

The appellant's statement of related proceedings appendix in the brief is correct. There are no decisions rendered by a court or the Board in any proceeding identified pursuant to paragraph (c) (1) (ii) of this section.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Brian Kwon:bk
November 07, 2006

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11/7/06

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German Patent No. DE 198 55 426 A1
(Offenlegungsschrift)

SUBSTANCE FOR USE IN THE TREATMENT AND PROPHYLAXIS OF RHEUMATIC AND ARTHRITIC DISORDERS AND IN THE PROPHYLAXIS OF CARDIOVASCULAR DISORDERS

Wolfgang Langhoff and Udo Laumann

UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. OCTOBER 2006
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SUBSTANCE FOR USE IN THE TREATMENT AND PROPHYLAXIS OF RHEUMATIC AND ARTHRITIC DISORDERS AND IN THE PROPHYLAXIS OF CARDIOVASCULAR DISORDERS

[Mittel zur Therapie und Prophylaxe von rheumatisch-arthritischen Erkrankungen und zur Prophylaxe von cardiovasculären Erkrankungen]

Inventors:	Same as Applicants
Applicants:	Wolfgang Langhoff and Udo Laumann

The following statements are taken [unedited] from the documents submitted by the applicant.

Description /2*

The present invention relates to a pharmaceutical composition, in particular a substance for use in the treatment and prophylaxis of rheumatic and arthritic disorders, in particular of rheumatism and arthritis, and in the prophylaxis of cardiovascular (heart and circulation) disorders, in particular of cardiac infarction, atherosclerosis stenosis and thrombosis. The rheumatic and arthritic disorders and the cardiovascular disorders have underlying inflammatory processes in common.

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* [Numbers in the margin indicate pagination of the original foreign text.]

In our society, disorders of the locomotor system and of the cardiovascular system constitute a considerable portion of the cases requiring treatment. Thus, the economic damage due to days not worked because of illness or early retirement is high.

The disorders listed above are manifestations that are autoimmunologically and genetically predisposed and that accompany and/or are initiated by small inflammatory processes in the body.

It is known that the daily ingestion of ω-3-unsaturated (polyunsaturated) fatty acids is partially responsible for reducing the inflammatory processes. Therefore, it has been observed that the ingestion of ω-3-unsaturated fatty acids leads to an anti-inflammatory effect while at the same time other effects, e.g., effects detrimental to the gastric system, are observed, and on ingestion of NSAIDs (nonsteroidal anti-inflammatory drugs), are absent. Overall, this leads to an improved quality of life since fewer medicinal products can be administered and therefore fewer adverse events typically observed with medicinal products occur, such as can develop for example, on administration of medicinal products of the NSAID type.

The cardiovascular disorders, such as cardiac infarction, atherosclerosis and stenosis, are also triggered and reinforced by local inflammatory processes. Bacterial infiltration (e.g., Chlamydia) can further aggravate these processes. In most cases, the precursor of thrombosis is atherosclerosis. Acetylsalicylic acid, which is known to be a platelet aggregation inhibitor, is only a weak inhibitor of the platelet function as well as only a weak antithrombocytic substance. Normally, doses of 75-160 mg/day are used to inhibit aggregation.

It is known that acetylsalicylic acid in a concentration of approximately 75 mg per person and per day promotes the formation of the highly effective endogenous, intracellular radical catcher ferritin. Ferritin is known to be a cytoprotective antioxidative protein that catches free iron ions in the cellular metabolism and thereby counteracts the oxygen-dependent radical formation, which has the effect that inflammatory processes which invariably involve radicals are not further aggravated.

Thus, one problem to be solved by the present invention is to make available a pharmaceutical composition which is improved with respect to its effect in the treatment and prophylaxis of inflammatory processes in the body, in particular its effect in the treatment and prophylaxis of rheumatic and arthritic disorders and in the prophylaxis of cardiovascular disorders.

Specifically, the present invention relates to a pharmaceutical composition comprising

(a) a minimum of one ω-3-unsaturated fatty acid and/or its physiologically acceptable derivatives,

(b) vitamin E,

(c) vitamin C, and

(d) acetylsalicylic acid.

The ω-3-unsaturated fatty acid used is preferably α-linolenic acid. Preferably, the present invention relates to a pharmaceutical composition comprising

(a) 70-82 wt% of a minimum of one ω-3-unsaturated fatty acid, in particular α-linolenic acid, and/or its physiologically acceptable derivatives,

(b) 7.5-13 wt% of vitamin E,

(c) 10-15 wt% of vitamin C, and

(d) 0.5-2 wt% of acetylsalicylic acid,

relative to the composition comprising (a), (b), (c) and (d).

Surprisingly, it was found that in the treatment and prophylaxis of rheumatic and arthritic disorders and in the prophylaxis of cardiovascular disorders, the combination of the active substances (a) to (d) is considerably more effective than the separate principal substances ω-3-unsaturated fatty acid (and/or its physiologically acceptable derivatives), vitamin E, vitamin C and acetylsalicylic acid.

Since acetylsalicylic acid according to the present invention is used in extremely low doses, i.e., lower than 75 mg/day, preferably lower than 60 mg/day, a platelet aggregation inhibiting effect, if any, is barely noticeable. As a result, none of the known adverse effects of acetylsalicylic acid, such as gastric hemorrhages or pseudoallergic reactions, occur. No other known product is able to lead to the anti-inflammatory effect achieved with the composition according to the present invention in the treatment of rheumatic, arthritic and cardiovascular disorder with such few adverse effects.

The composition according to the present invention is intended for oral administration and can be used in the form of a powder, a tablet, a sugar-coated pill, a capsule, a solution, a concentrate, a syrup, a suspension, a gel or in the form of a dispersion.

The composition according to the present invention is dosed to ensure that the total quantity of acetylsalicylic acid (d) administered to the body is between 30 and 75 mg per day, preferably between 35 and 45 mg per day, and especially between 35 and 40 mg per day (for person with a body weight of approximately 75 kg). The quantitative content of components (a), (b) and (c) can be computed based on the percentages given for each component above. The composition according to the present invention can be administered in several separate doses distributed over the day. In addition, it is also possible to administer components (a) to (d) not only as a mixture but also separately. In such a case, the combination of active substances can be made available in such a way that the individual components are provided in separate form and can be either mixed prior to administration or can be administered separately (kit of parts). /3

The ω-3-unsaturated fatty acids can be used in pure form or in the form of their physiologically acceptable derivatives, in particular in the form of their esters. The

physiologically acceptable esters of the ω-3-unsaturated fatty acids preferably are their mono-, di- and triglycerides or their alkyl esters with 1-4 C atoms, in particular ethyl esters. The ω-3-unsaturated fatty acid and their derivatives preferably are metabolized in the body to form prostaglandins.

The ω-3-unsaturated fatty acids are selected especially from the group comprising α-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid or mixtures thereof. The ω-3-unsaturated fatty acids can be used not only in pure form but also, as already mentioned above, in the form of their physiologically acceptable synthetic or naturally occurring derivatives, in particular the glycerol esters or the alkyl esters with 1-4 C atoms. The source of the naturally occurring derivatives of the ω-3-unsaturated fatty acids, in particular of the triglycerides, especially worth mentioning includes above all wheat germ oil, soybean oil, walnut oil and rapeseed oil.

The source of α-linolenic acid especially worth mentioning includes above all hempseed oil (which contains approximately 25-30% of α-linolenic acid) and linseed oil (which contains approximately 35-70% of linolenic acid), the source of eicosapentaenoic acid and docosahexaenoic acid includes in particular fish oils or concentrates thereof. The naturally occurring sources contain the ω-3-unsaturated fatty acids or the derivatives thereof preferably in a quantity of at least 10%.

The fish oils to be used according to the present invention are in particular those that contain approximately 10-35% of eicosapentaenoic acid and docosahexaenoic acid each. The fish oils to be used are in particular cod liver oil and salmon oil and their concentrates. As a rule, it is possible to use all sources of ω-3-unsaturated fatty acids and their derivatives that the body converts into prostaglandins.

According to the present invention, at least one ω-3-unsaturated fatty acid in pure form or in the form of its physiologically acceptable derivatives is used; however, it is also possible to use mixtures of ω-3-unsaturated fatty acids or mixtures of ω-3-unsaturated fatty acids with their physiologically acceptable derivatives.

The composition according to the present invention contains 70-82 wt%, preferably 75-80 wt%, of the ω-3-unsaturated fatty acids, in particular α-linolenic acid or its physiologically acceptable natural or synthetic derivatives, especially of the esters mentioned above, relative to the composition comprising (a), (b), (c) and (d). If sources of ω-3-unsaturated fatty acids, e.g., the above-mentioned natural oils containing the triglycerides of the ω-3-unsaturated fatty acids are used, the quantities mentioned refer to the quantity of the source used.

Vitamin E is used in pure form. The composition according to the present invention contains 7.5-13 wt%, preferably 7.5-8.5 wt%, of vitamin E, relative to the composition comprising (a), (b), (c) and (d).

Vitamin C is used in pure form. The composition according to the present invention contains 10-15 wt%, preferably 12-15 wt%, of vitamin C, relative to the composition comprising (a), (b), (c) and (d).

Acetylsalicylic acid is used in pure form. The composition according to the present invention contains 0.5-2.0 wt%, preferably 0.5-1.5 wt%, of acetylsalicylic acid, relative to the composition comprising (a), (b), (c) and (d). Acetylsalicylic acid is preferably used in the form of an enteric coated formulation, i.e., a formulation that does not release the active substance in the stomach but in the small intestine instead, e.g., in the form of a conventional microencapsulated dosage known from the prior art.

Furthermore, the composition according to the present invention may, additionally and independently of one another, also contain physiologically acceptable quantities of coenzyme Q, beta-carotene, biologically active selenium, one or more water-soluble vitamins, physiologically valuable elements, garlic and/or hawthorn extract, and components that are commonly used in the formulation (galenic pharmacy).

Merely by way of an example, it should be mentioned that the composition according to the present invention, relative to 100 parts by weight of the composition comprising (a), (b), (c) and (d), may additionally contain:

- 0.1-0.5 parts by weight, preferably 0.2-0.4 parts by weight, of coenzyme Q;
- 0.1-0.4 parts by weight, preferably 0.2-0.3 parts by weight, of beta-carotene;
- 6×10^{-4} to 8×10^{-4} parts by weight, preferably 6.5×10^{-4} to 7.5×10^{-4}, parts by weight of biologically active selenium;
- one or more of the water-soluble vitamins thiamine, riboflavin, niacin, pyridoxine, pantothenic acid, biotin, cobalamin and folic acid, in particular in the parts by weight listed in the table* below.

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*[In tables, equations, and figures, commas in numbers denote decimal points.]

(1) Vitamine	(2) von	(3) bis	(4) bevorzugt von	(5) bevorzugt bis
(6) Thiamin	0,01	0,1	0,02	0,09
(7) Riboflavin	0,01	0,1	0,02	0,09
(8) Niacin	0,1	1,0	0,2	0,9
(9) Pyridoxin	0,01	0,1	0,02	0,09
(10) Panthotensäure	0,05	0,5	0,1	0,4
(11) Biotin	$3*10^{-5}$	$6*10^{-5}$	$4*10^{-5}$	$5*10^{-5}$
(12) Cobalamin	$1*10^{-4}$	$4*10^{-4}$	$2*10^{-4}$	$3*10^{-4}$
(13) Folsäure	$1*10^{-2}$	$4*10^{-2}$	$2*10^{-2}$	$3*10^{-2}$

Key: 1 Vitamins
2 From
3 To
4 Preferably from
5 Preferably to
6 Thiamine
7 Riboflavin
8 Niacin
9 Pyridoxine
10 Pantothenic acid
11 Biotin
12 Cobalamin
13 Folic acid

- one or more of the elements in their physiologically acceptable form, selected from the group comprising magnesium, iron, copper, iodine, manganese, zinc, molybdenum and chromium, in particular in the parts by weight listed in the table below:

(1) Element	(2) von	(3) bis	(4) bevorzugt von	(5) bevorzugt bis
Mg	0,01	0,1	0,02	0,09
Fe	0,01	0,02	0,015	0,017
Cu	$1,0*10^{-3}$	$2*10^{-3}$	$1,1*10^{-3}$	$1,9*10^{-3}$
I	$2*10^{-4}$	$3*10^{-4}$	$2,2*10^{-4}$	$2,8*10^{-4}$
Mn	$3*10^{-3}$	$4*10^{-3}$	$3,2*10^{-3}$	$3,8*10^{-3}$
Zn	0,01	0,02	0,011	0,019
Mo	$1*10^{-4}$	$2*10^{-4}$	$1,1*10^{-4}$	$1,9*10^{-4}$
Cr	$1*10^{-4}$	$2*10^{-4}$	$1,1*10^{-4}$	$1,9*10^{-4}$

Key: 1 Element
2 From
3 To
4 Preferably from
5 Preferably to

- and other conventionally used components, such as antioxidants, dispersing and/or suspending substances and additional aids commonly used in galenic pharmacy, such as flavoring substances, dyes, thickening substances and conventionally used physiologically safe separating substances.

Relative to 100 parts by weight of the overall composition comprising (a), (b), (c) and (d), the composition according to the present invention may also contain

- 0.1-0.5 parts by weight, preferably 0.2-0.4 parts by weight, of garlic extract,
- 0.1-0.5 parts by weight, preferably 0.2-0.4 parts by weight, of hawthorn extract, or
- 0.1-1.0 part by weight, preferably 0.2-0.9 parts by weight, of combinations of garlic and hawthorn extract.

The pharmaceutical composition described above is suitable for use in the prophylaxis and/or treatment of inflammations in the human or animal body. In particular, the composition according to the present invention is suitable for use in the prophylaxis and treatment of rheumatic and arthritic disorders and in the prophylaxis of cardiovascular disorders. The rheumatic and arthritic disorders include, in particular, rheumatism and arthritis, and the cardiovascular (heart and circulation) disorders include, in particular, cardiac infarction, atherosclerosis, stenosis and thrombosis. Atherosclerosis is a precursor of thrombosis.

The composition according to the present invention can be used in methods for the preparation of medicinal products in which this composition is used to treat and/or prevent the disorders mentioned above and can subsequently be used in the doses mentioned above.

In connection with the composition according to the present invention, it was surprisingly found that the combination of ω-3-unsaturated fatty acids, or their physiologically acceptable derivatives mentioned above, vitamin E and vitamin C with acetylsalicylic acid, said acetylsalicylic acid overall being used in a very low dose, leads to an effect that enhances the anti-inflammatory action, i.e., to a synergistic effect. The administration of a combination of ω-3-unsaturated fatty acids (and/or their derivatives mentioned above), vitamin E, vitamin C and acetylsalicylic acid leads to a superior anti-inflammatory effect when compared to the administration of ω-3-unsaturated fatty acids (or their derivatives mentioned above), vitamin E, vitamin C or acetylsalicylic acid in the form of separate components. Thus, the compositions according to the present invention are especially suitable as substances for use in the treatment and therapy of rheumatic and arthritic disorders and for use in the prophylaxis of cardiovascular disorders.

The present invention will be illustrated in greater detail based on the examples below, without intending to restrict the invention in any way.

Example /5

In the example below, cod liver oil, vitamin E, vitamin C and acetylsalicylic acid, each in commercially available pure form, were used. An experiment in which linseed oil was used as the source for the ω-3-unsaturated fatty acid (α-linolenic acid) led to identical results.

In the test, the anti-inflammatory effect of the following formulations was compared after administration to a person (body weight approximately 75 kg) suffering primarily from a rheumatic and/or arthritic disorder as well as from a mild cardiovascular disorder:

A) 10 g of cod liver oil,
1000 mg of vitamin E, and
1000 mg of vitamin C,

B) 80 mg of acetylsalicylic acid,

C) 250 mg of vitamin E and
40 mg of acetylsalicylic acid,

D) 50% of A and 50% of B).

The overall amount listed above was administered daily, optionally in single doses, over a period of 14 weeks. Using a rating scale (1 = excellent, 2 = good, 3 = satisfactory, 4 = adequate, 5 = barely noticeable improvement, 6 = no improvement), the test subject described the effect of the above compositions as follows:

① Zusammensetzung	Bewertung ②
A	2
B	6
C	3
D	1

Key: 1 Composition
2 Rating

It was found that the oral administration of composition A), B) or C) by itself was less effective (led to a lesser improvement) than the administration of D). After the administration of composition D) according to the present invention, it was possible to observe a synergistic effect which exceeds the effect to be expected. The combination of A) and B), which constitutes composition D), is considerably improved when compared to the single components A), B) or C) used in the same quantity.

Claims

1. A pharmaceutical composition comprising

(a) a minimum of one ω-3-unsaturated fatty acid and/or its physiologically acceptable derivatives,

(b) vitamin E,

(c) vitamin C, and

(d) acetylsalicylic acid.

2. The composition as in Claim 1, characterized in that the composition contains

(a) 70-82 wt% of ω-3-unsaturated fatty acids and/or their physiologically acceptable derivatives,

(b) 7.5-13 wt% of vitamin E,

(c) 10-15 wt% of vitamin C, and

(d) 0.5-2 wt% of acetylsalicylic acid,

relative to the composition comprising (a), (b), (c) and (d).

3. The composition as in Claim 1 or 2, characterized in that the ω-3-unsaturated fatty acids are used in pure form, in the form of their mono-, di- or triglycerides, or in the form of their alkyl esters with 1-4 C atoms.

4. The composition as in Claim 1, characterized in that the ω-3-unsaturated fatty acid is selected from the group comprising α-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid or mixtures thereof.

5. The composition as in any one of Claims 1-4, characterized in that it contains the ω-3-unsaturated fatty acid in the form of its triglycerides as contained in linseed oil, hempseed oil, wheat germ oil, soybean oil, walnut oil, rapeseed oil, fish oil or mixtures thereof.

6. The composition as in Claim 5, characterized in that the fish oil is selected from the group comprising salmon oil and cod liver oil.

7. The composition as in any one of Claims 1-6, characterized in that, in addition, the composition also contains coenzyme Q, beta-carotene, biologically active selenium, one or more water-soluble vitamins, or mixtures of these components.

8. The composition as in any one of Claims 1-7, characterized in that, in addition, it also contains garlic extract and/or hawthorn extract.

9. The composition as in Claim 8, characterized in that the total quantity of garlic extract and/or hawthorn extract in the pharmaceutical composition measures 0.1-1.0 part by weight, relative to 100 parts by weight of the composition comprising (a), (b), (c) and (d).

10. The composition as in any one of Claims 1-9, characterized in that, in addition, it also contains beta-carotene, folic acid and biologically active selenium. /6

11. The composition as in Claim 10, characterized in that, relative to 100 parts by weight of (a), (b), (c) and (d), it contains

0.1 to 0.5 parts by weight of beta-carotene,

1×10^{-2} to 4×10^{-2} parts by weight of folic acid, and

6×10^{-4} to 8×10^{-4} parts by weight of biologically active selenium.

12. The composition as in any one of Claims 1-11, characterized in that it can be administered in a dose of 30-75 mg of acetylsalicylic acid per person and per day.

13. A substance comprising the composition as in any one of Claims 1-12 for use in the treatment of inflammations in the human or animal body.

14. The substance as in Claim 13 for use in the treatment and prophylaxis of rheumatic and arthritic disorders or in the prophylaxis of cardiovascular disorders.

15. The substance as in Claim 14 for use in the treatment and prophylaxis of rheumatism and arthritis and in the prophylaxis of cardiac infarction, atherosclerosis, stenosis and/or thrombosis.

16. The use of the composition as defined in any one of Claims 1-12 for use in the treatment of inflammatory disorders of the human or animal body.

17. The use as in Claim 16 for use in the treatment and prophylaxis of rheumatic and arthritic disorders and/or in the prophylaxis of cardiovascular disorders.

18. The use as in Claim 17 for use in the treatment and prophylaxis of rheumatism and arthritis and in the prophylaxis of cardiac infarction, atherosclerosis, stenosis and thrombosis.

19. The use as in any one of Claims 16-18 in a dose of 30-75 mg of acetylsalicylic acid per person and per day.

20. The use of the composition as defined in any one of Claims 1-12 for use in the production of a medicinal product for use in the treatment and/or prophylaxis of cardiovascular disorders.